

REMARKS**I. Claim Status:**

Claims 4-15 are pending and stand twice rejected. Claims 1, 2, 6 and 16-26 have been canceled previously and herein without prejudice. Claims 4, 5 and 14 have been amended as described more fully herein. Support for the amendment to claim 4 is found in the Specification at pg. 8, lines 19-20, pg. 9, lines 8-13, paragraphs 31, 32, 34 and 57, and more generally throughout the Specification. Support for the amendments to claims 5 and 14 is found throughout the Specification. With respect to claim 14, specific support is found at pg. 7, line 20. No new subject matter has been added by the amendments. Entry and consideration are respectfully requested.

II. Claim Objections:

Claim 14 is objected to for use of the phrase, "word line." Claim 14 has been amended to recite "word line" as a parenthetical alternative description of "row." Accordingly, reconsideration and removal of the objection to claim 14 are respectfully requested.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph:

Claim 4 stands rejected under § 112, second paragraph, as being indefinite for use of the phrase, "means to electrically connect." The phrase has been amended to recite proper 35 U.S.C. § 112, second paragraph form. Accordingly, reconsideration and removal of the rejection of claim 4 under § 112, second paragraph are respectfully requested.

Claim 5 stands rejected under § 112, second paragraph as being indefinite for

use of the term “couple.” Claim 5 has been amended to recite “pair” in place of “couple” to specifically recite the number of parallel external connectors. Accordingly, reconsideration and removal of the rejection of claim 5 under § 112, second paragraph are respectfully requested.

IV. Rejections Under 35 U.S.C. § 102(e):

Claims 4, 5 and 7-11 remains rejected under § 102(e) as being anticipated by Xu et al. (U.S. 20050112544). Applicants again respectfully traverse the rejections.

As previously explained, Xu et al. discloses an apparatus for detecting cells and/or molecules with electrodes. Detection is accomplished by measuring impedance changes due to the presence of cells and/or molecules. *See generally* Abstract. Impedance changes are described as occurring with changes in the population of cells and/or molecules adhering or binding to the electrodes. [0024]. The apparatus uses a series of electrode arrays, each array comprising two or more electrodes separated by non-conductive material and may include a plurality of evenly spaced electrode pairs. [0023-0026]; [0032]; [0192] and [0198]. Notably, electrodes are described throughout the Xu et al. application as being in pairs, at a minimum.

The finding in the office action that “Xu additionally teaches in paragraphs [0192] and [0198] that each microelectrode within the array is individually addressed and in communication with a switching system using conductive traces (Figure 1A:130) and conductive pads (Figure 1A:150)” mischaracterizes the specific disclosure of Xu. Both paragraphs recite, “at least one ***pair*** of the electrodes or one ***pair*** of electrode arrays of the present apparatuses are individually addressed in terms of connecting to an impedance analyzer Impedances are measured

between such a **pair** of electrodes or such a **pair** of electrode structures

'Individually addressed' means that the electrode impedance can directly be connected to such a **pair** of electrodes or electrode structures." [0192]. Figure 1A is consistent with this disclosure.

Xu further discloses, "[t]he electrodes or electrode structures comprised in the present microplate can be arranged in any suitable ways. In one example, at least one **pair** of the electrodes or one **pair** of electrode structures of at least one device is individually addressed in terms of connecting to an impedance measurement circuit." [0198]

It is irrefutable these passages and drawing disclose the measurement of electric impedance between microelectrode structures within the *same* microelectrode structure unit. It is further irrefutable the microelectrode pairs or microelectrode structure units occupy, and are dedicated to, a specific well of the array. In this manner the microelectrode pairs or microelectrode structure units are adjacent one another.

Claim 4, as amended, incorporates the limitations of claim 6 (now canceled), and specifically recites each microelectrode as being adapted for connection to a single cell and as being part of a planar array of microelectrodes that defines an array region. A pair of reference electrodes in planar orientation to the microelectrode array is positioned *outside* the array region.

Xu clearly does not show or suggest a biochip having microelectrodes forming a planar array with each microelectrode dedicated to an individual cell and selectively/individually driven. Quite to the contrary, Xu discloses paired electrodes being driven as pairs and addressed as pairs. Moreover, Xu does not show or suggest reference electrodes positioned outside a defined array region occupied by

the array of microelectrodes that provide a reference point to establish the voltage to be introduced to the individually driven microelectrodes so as to establish a different electrical field in the electrolyte.

For all these reasons, Xu et al. cannot properly be considered to anticipate claim 4 as it does not disclose each and every element of claim 4, and is not enabling. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006), *reh'g en banc denied*, 469 F.3d 1039 (Fed. Cir. 2006)(for a prior art reference to anticipate a claim, it must disclose all the limitations of the claimed invention and be enabled, i.e., its disclosure must be sufficient to allow one of ordinary skill in the art to make and use the claimed invention). Xu et al. falls far short of this standard.

The argument that, “[b]ecause Xu teaches in paragraph [0147] that each microelectrode structure occupies a size ‘less than 50 micron by 50 micron,’ it is understood that each microelectrode may be in communication with only a single cell (especially when the cells of interest are larger than 50 microns in diameter)” is equally without merit. To suggest the electrodes communicate with a single cell due to the apparent similar size of the electrodes and cells equates area with three-dimensional spatial orientation. The two are mutually distinct concepts. There is no such teaching or suggestion in Xu.

Similarity of area does not in any way explain three-dimensional orientation. To the contrary, as the electrodes of Xu are not aligned in a planar configuration, but merely positioned at the bottom of individual wells of a multi-well plate, [0038] and [0040], the most likely orientation is that multiple cells surround and communicate with each microelectrode and that each cell likely communicates with multiple electrodes, particularly when the microelectrodes are arranged and controlled in pairs. One microelectrode can easily be overlapped by portions of a number of cells

without any dedication to a specific cell, and vice versa. The Xu apparatus as disclosed is not designed to have the same granular/specificity level of individual microelectrode/cell communication as disclosed and claimed by Applicants.

As previously stated, Applicants' claimed invention, specifically independent claim 4, requires individual electrodes dedicated to individual cells to monitor cells on an individual level rather than as a colony or as a grouping. Xu et al. does not show or suggest such an electrode/cell configuration. Absent this feature and for all the foregoing reasons, Xu et al. cannot properly be considered to anticipate claim 4. Accordingly, reconsideration and removal of the rejection of claim 4 are respectfully requested.

Claims 5 and 7-11 depend directly, or ultimately, from claim 4 and are allowable for the same reasons as those given in support of claim 4. Accordingly, reconsideration and removal of the rejection of claims 5 and 7-11 are respectfully requested.

V. Rejections under 35 U.S.C. § 103(a):

Claims 4, 5 and 7-11 stand rejected under § 103(a) as being obvious over Xu et al. in view of Johnson (US 7,521,224). Applicants respectfully traverse the rejections.

Claim 4, for the reasons previously stated, is neither anticipated nor rendered obvious by Xu. Johnson does not fill the deficiencies of Xu.

Johnson is directed to an electroporation apparatus to facilitate the controlled introduction of genes, drugs and chemicals into cells cultured on an array to allow rapid parallel analysis. [3:11-13]. The method is distinguished from prior art methods in that subpopulations of cells are loaded with one gene and other

subpopulations are loaded with a different gene. [8:6-10]. Regions of the array are selectively electroporated to enable imaging techniques, e.g., fluorescent assays, to determine the cellular effects of the introduced substances. See generally, Col. 7, l. 28-Col. 8, l. 5.

Solutions carrying the genes, drugs, etc., are introduced into a perfusion chamber preferably having a transparent top to enable imaging analysis. [4:51-54]. The chamber contains all the cultured cells so that the entire population of cells is exposed to the solution in an indiscriminate manner. The electroporation process is achieved by applying an electric field across a cathode and an anode as shown in FIG. 2. [4:42-45]. The array is broken down into regions that are selectively electroporated. [4:51-56]. Thus, each array region has a least one cathode and at least one anode electrode, and the cells are electroporated based upon their location in a specific region of the chamber array. Each cell is in communication with at least one cathode and at least one anode in the array region.

The electrodes are comprised of glass optical fiber bundles bonded with a biocompatible epoxy to form microwires. The microwires of the electrode protrude from the surface of the electrode and create spaces into which the cells migrate and adhere. This prevents the cells from being flushed away when solutions flow through the perfusion chamber. Multiple microwires are dedicated to each array unit cell or array region. See generally, Col. 6, l. 19-51. Based on this construction, each cell in an array region is exposed to, and in communication with multiple, variably-oriented microwires.

With respect to the orientation of the charged electrode to the reference electrode, Johnson describes reference electrodes within the same array region as the charged electrode, FIGS. 5A, 5B and 5C, or a large exterior reference electrode

placed above all the array regions, FIG. 5D.

Johnson fails to fill the deficiencies of Xu on a number of grounds. As shown in FIG. 2, the charged electrode and the reference electrode are both connected to the same cell. As each cell can occupy only one array region, the charged and reference electrodes must be in the same array region. Applicants' invention has the reference electrode positioned outside the array region in a planar orientation to the microelectrodes.

Because of the very small size of the Johnson microwires, multiple microwires are energized or activated as Johnson does not disclose or suggest individual control of each microwire. Thus, multiple microwires in a bundle are activated together and communicate with each cell together. Each microwire is not dedicated to a single cell and each cell does not have a single microwire dedicated to it. In the embodiment using a large reference electrode, Johnson does not disclose a reference electrode in a planar orientation relative to the array of microelectrodes.

For all the foregoing reasons, Xu in view of Johnson does not render claim 4 obvious. Claims 5 and 7-11 depend directly, or ultimately, from claim 4 and are allowable for the same reasons as those given in support of claim 4. Accordingly, reconsideration and removal of the rejection of claims 5 and 7-11 under § 103(a) are respectfully requested.

Claims 6 and 15 stand rejected under 35 U.S.C. § 103(a) as being obvious over Xu as applied to claims 5 and 11 in view of Sugihara. Claim 6 has been canceled thereby rendering the rejection thereof moot. Applicants respectfully traverse the rejection of claim 15. Claim 15 depends ultimately from claim 4 and is therefore allowable for the same reasons given for claim 4. Sugihara et al. does not fill the deficiencies of Xu et al. for the following reasons.

As previously stated, Sugihara et al. discloses a cell potential measuring electrode assembly that employs reference electrodes separated from other electrodes used to take impedance measurements. The reference electrodes are not introduced to the cell cultures being measured thereby reducing noise and allowing for more precise measurements. [2:35-62]. It is noteworthy that Sugihara et al. is not directed to an assembly for use in cell electroporation.

Sugihara et al. does not disclose, or even suggest, a planar array of microelectrodes in which each microelectrode is individually driven and adapted to connect to single cell. To the contrary, Sugihara et al. discloses measuring cell potentials using all the microelectrodes. [2:64-67]. Absent any teaching, suggestion, or motivation to dedicate individual microelectrodes to a single cell so as to perform electroporation of the individual cell, Sugihara et al. does not render claim 15 obvious alone, or in combination with Xu et al. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejection of claim 15 under § 103(a).

Claim 12 stands rejected under § 103(a) as being obvious over Xu et al. as applied to claim 11, and further in view of Casnig (US 5,134,070). Applicants respectfully traverse the rejection.

Claim 12 depends ultimately from claim 4 and is therefore allowable for the same reasons given for claim 4. As stated, claim 4 recites a planar array of microelectrodes in which each microelectrode is individually driven and adapted to connect to single cell.. Xu et al. does not show or suggest such a feature. Casnig is equally deficient for the following reasons.

Casnig discloses a method and device for inducing electroporation of a monolayer of cells. The apparatus includes a Petri-like dish with an electrically-

conductive substrate on which the cells are grown. At least one electrode attached to a bottom surface of the substrate provides a conduit for the introduction of electric current to perform the electroporation. Based on the apparatus and method disclosed, the opposing and detection electrodes of Casnig facilitate electroporation, and detection of the effects of electroporation, in a plural, nondiscriminatory manner- all cells are treated as a group or colony rather than on an individual basis. See *generally* Summary of the Invention [3:36-4:19]

Casnig does not disclose, or even suggest, a planar array of microelectrodes, each microelectrode dedicated to a single cell. To the contrary, Casnig discloses measuring cell potentials as a group using detector microelectrodes. [4:16-19]. Absent any teaching, suggestion, or motivation to construct a planar array of microelectrodes with each microelectrode selectively driven and adapted for connection to a single cell so as to perform electroporation of the individual cell, Casnig does not render claim 12 obvious alone, or in combination with Xu et al.. Accordingly, for all the foregoing reasons, Applicants again respectfully request reconsideration and removal of the rejection of claim 12 under § 103(a).

Claims 13 and 14 stand rejected under § 103(a) as being obvious over Xu et al. as applied to claim 11, and further in view of Gomez et al. (US 2003/0157587). Applicants respectfully traverse the rejection.

Claims 13 and 14 depend ultimately from claim 4 and are allowable for the same reasons as those given in support of claim 4. As stated, the microelectrodes recited in claim 4 are organized in a planar array and are each connected to a single cell and selectively driven to perform electroporation of a single cell. Xu et al. does not show or suggest such a feature. Gomez et al. is equally deficient for the following reasons.

Gomez et al. discloses a method and biochip for collecting a microbiological entity of interest with a non-uniform electric field created by electrically pulsing electrodes in a collection chamber to capture the specimen via dielectrophoresis. Collection electrodes deliver the electric current to capture the desired microbiological entity and may also perform a detection function. In an alternative embodiment, dedicated detection electrodes may be placed in the containment chamber. [0036]. Similar to the other cited references, Gomez et al. does not disclose a planar array of microelectrodes in which each electrode is adapted for connection to a single cell. Apart from this glaring deficiency, it should also be noted Gomez et al. is not directed to electroporation and should not be considered analogous art.

Gomez et al. does not disclose, or even suggest, the construction of a planar array of microelectrodes, each dedicated to individual cells or molecules. To the contrary, Gomez et al. discloses collection and/or detection electrodes that measure microbiological entities as a group. In fact, Gomez et al. describes using a carrier element disposed on the collection electrodes to entrain the microbiological species and concentrate it at the point of measurement. [0034-0035]. Therefore, Gomez et al. teaches the collection of multiple cells or molecules on a single electrode, which teaches away from Applicants' claimed invention.

Absent any teaching, suggestion, or motivation to construct a planar array of microelectrodes in which each microelectrode is adapted for connection to a single cell so as to perform electroporation of the individual cell, Gomez et al. does not render claims 13 and 14 obvious alone, or in combination with Xu et al.. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejections of claims 13 and 14 under § 103(a).

Claims 6 and 15 stand rejected under 35 U.S.C. § 103(a) as being obvious over Xu and Johnson as applied to claims 5 and 11 further in view of Sugihara. Claim 6 has been canceled thereby rendering the rejection thereof moot. Applicants respectfully traverse the rejection of claim 15. Claim 15 depends ultimately from claim 4 and is therefore allowable over Xu et al. and Johnson for the same reasons given for claim 4. Sugihara et al. does not fill the deficiencies of Xu et al. or Johnson for the following reasons.

As previously stated, Sugihara et al. discloses a cell potential measuring electrode assembly that employs reference electrodes separated from other electrodes used to take impedance measurements. The reference electrodes are not introduced to the cell cultures being measured thereby reducing noise and allowing for more precise measurements. [2:35-62]. It is noteworthy that Sugihara et al. is not directed to an assembly for use in cell electroporation.

Sugihara et al. does not disclose, or even suggest, a planar array of microelectrodes in which each microelectrode is individually driven and adapted to connect to single cell. To the contrary, Sugihara et al. discloses measuring cell potentials using all the microelectrodes. [2:64-67]. Absent any teaching, suggestion, or motivation to dedicate individual microelectrodes to a single cell so as to perform electroporation of the individual cell, Sugihara et al. does not render claim 15 obvious alone, or in combination with Xu et al. and Johnson. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejection of claim 15 under § 103(a).

Claim 12 stands rejected under § 103(a) as being obvious over Xu et al. and Johnson as applied to claim 11, and further in view of Casnig (US 5,134,070). Applicants respectfully traverse the rejection.

To reiterate, claim 12 depends ultimately from claim 4 and is therefore allowable for the same reasons given for claim 4. As stated, claim 4 recites a planar array of microelectrodes in which each microelectrode is individually driven and adapted to connect to single cell.. Xu et al. and Johnson do not show or suggest such a feature. Casnig is equally deficient for the following reasons.

As previously stated, Casnig discloses a method and device for inducing electroporation of a monolayer of cells. The apparatus includes a Petri-like dish with an electrically-conductive substrate on which the cells are grown. At least one electrode attached to a bottom surface of the substrate provides a conduit for the introduction of electric current to perform the electroporation. Based on the apparatus and method disclosed, the opposing and detection electrodes of Casnig facilitate electroporation, and detection of the effects of electroporation, in a plural, nondiscriminatory manner-all cells are treated as a group or colony rather than on an individual basis. See *generally* Summary of the Invention [3:36-4:19]

Casnig does not disclose, or even suggest, a planar array of microelectrodes, each microelectrode dedicated to a single cell. To the contrary, Casnig discloses measuring cell potentials as a group using detector microelectrodes. [4:16-19]. Absent any teaching, suggestion, or motivation to construct a planar array of microelectrodes with each microelectrode selectively driven and adapted for connection to a single cell so as to perform electroporation of the individual cell, Casnig does not render claim 12 obvious alone, or in combination with Xu et al. and Johnson. Accordingly, for all the foregoing reasons, Applicants again respectfully request reconsideration and removal of the rejection of claim 12 under § 103(a).

Claims 13 and 14 stand rejected under § 103(a) as being obvious over Xu et al. and Johnson as applied to claim 11, and further in view of Gomez et al. (US

2003/0157587). Applicants respectfully traverse the rejection.

As stated herein, claims 13 and 14 depend ultimately from claim 4 and are allowable for the same reasons as those given in support of claim 4.

Microelectrodes recited in claim 4 are organized in a planar array and are each connected to a single cell and selectively driven to perform electroporation of a single cell. Neither Xu et al. nor Johnson show or suggest such a feature. Gomez et al. is equally deficient for the following reasons.

Gomez et al. discloses a method and biochip for collecting a microbiological entity of interest with a non-uniform electric field created by electrically pulsing electrodes in a collection chamber to capture the specimen via dielectrophoresis. Collection electrodes deliver the electric current to capture the desired microbiological entity and may also perform a detection function. In an alternative embodiment, dedicated detection electrodes may be placed in the containment chamber. [0036]. Similar to the other cited references, Gomez et al. does not disclose a planar array of microelectrodes in which each electrode is adapted for connection to a single cell. Apart from this glaring deficiency, it should also be noted Gomez et al. is not directed to electroporation and should not be considered analogous art.

Gomez et al. does not disclose, or even suggest, the construction of a planar array of microelectrodes, each dedicated to individual cells or molecules. To the contrary, Gomez et al. discloses collection and/or detection electrodes that measure microbiological entities as a group. In fact, Gomez et al. describes using a carrier element disposed on the collection electrodes to entrain the microbiological species and concentrate it at the point of measurement. [0034-0035]. Therefore, Gomez et al. teaches the collection of multiple cells or molecules on a single electrode, which

teaches away from Applicants' claimed invention.


Absent any teaching, suggestion, or motivation to construct a planar array of microelectrodes in which each microelectrode is adapted for connection to a single cell so as to perform electroporation of the individual cell, Gomez et al. does not render claims 13 and 14 obvious alone, or in combination with Xu et al. and Johnson. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejections of claims 13 and 14 under § 103(a).

VI. Conclusion:

For all the foregoing reasons, the claims are considered to define patentably over the prior art. Reconsideration is requested and favorable action is solicited.

Respectfully Submitted,

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